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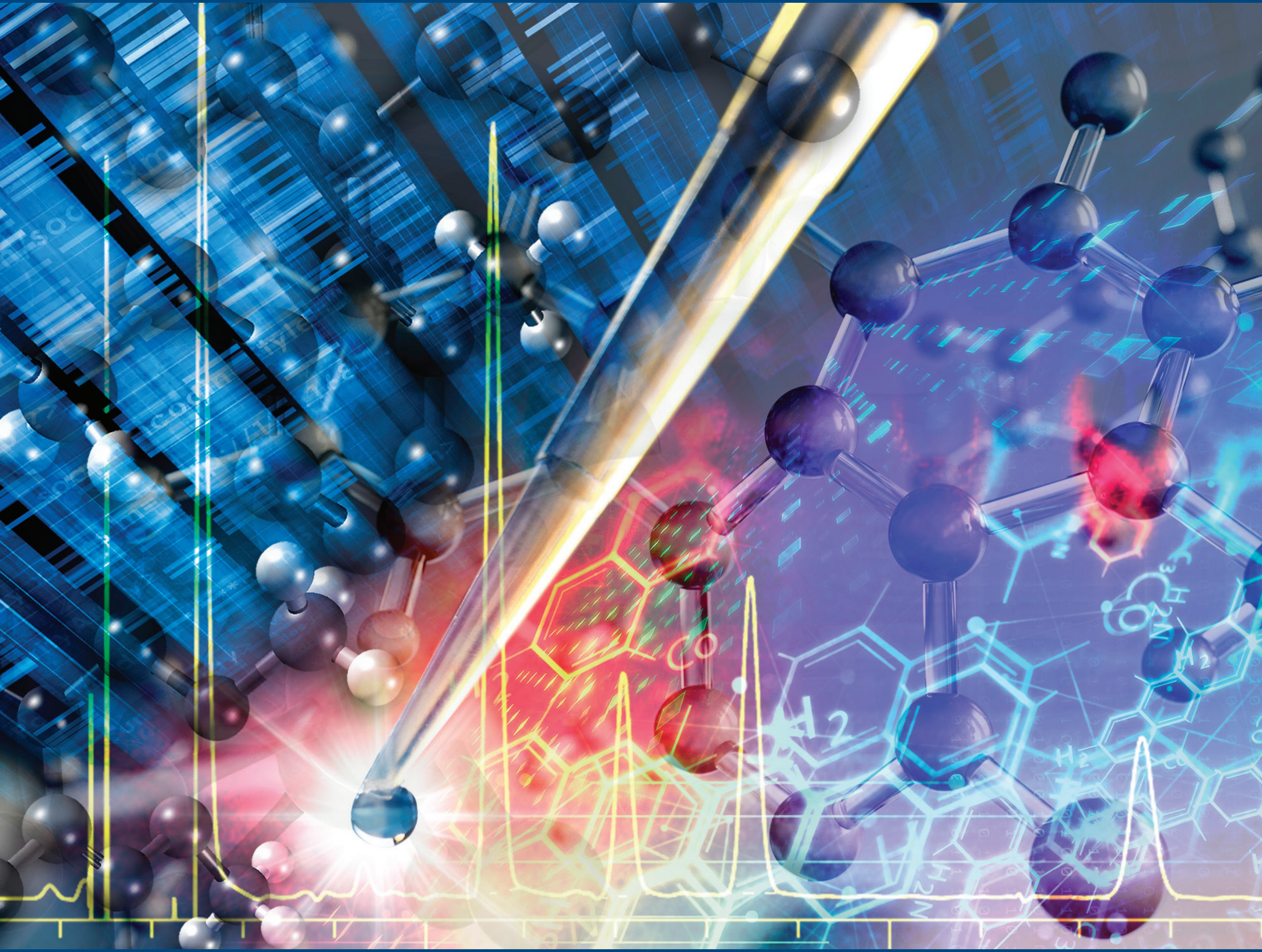

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ORIGINAL ARTICLE OPEN ACCESS

Preparation of Zwitterionic Silica-Based Sorbents for Simultaneous Extraction of Acidic and Basic Pharmaceuticals From Water Samples

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Keywords: environmental water samples | mixed-mode ion-exchange sorbent | pharmaceuticals | silica sorbent | zwitterionic functional group

ABSTRACT

The sol-gel approach was applied to develop three homemade silica sorbents. These sorbents where functionalized with mixed-mode zwitterionic exchange groups using only one additive to introduce at once the strong cation- (sulfonic groups) and strong anion-exchange (quaternary amines) moieties.

The developed materials were applied for the solid-phase extraction (SPE) of basic and acidic pharmaceuticals, and the sorbent functionalized with 2-(methacryloxy)-ethyldimethyl-3-(sulfopropyl)ammonium hydroxide was the best performing one. The optimal conditions for SPE were pH 5, a variable loading volume (ranging from 25 to 100 mL depending on the complexity of the sample) and elution volume with 5 mL of 1% NH_4OH in MeOH.

The method validation was carried out attending to apparent and relative recoveries, matrix effect, precision (intraday and interday), and detection and quantification limits. It can be highlighted that apparent recoveries were higher than 30% for most compounds and method detection limits were at the low ng/L. The validated method was applied to quantify the pharmaceuticals in environmental water samples.

1 | Introduction

Traditionally there have been two main types of extraction sorbents for sorptive extraction: organic polymer-based sorbents and inorganic silica-based sorbents. Organic polymer-based sorbents have a wider pH tolerance and may suffer swelling effects when exposed to organic solvents [1–4]. On the other hand, silica-based sorbents have high organic solvent resistance and mechanical stability but may be damaged at extreme pH [5–7]. One of the main advantages of silica-based sorbents is the ease to modify to introduce a wide variety of functional groups such as quaternary amines [8, 9], humic acids [10], or aliphatic chains (C_{12} and C_{18}) [11, 12].

Sorbents applied in extraction techniques are classified depending on the interactions they perform with the analytes, like reversed-phase, hydrophilic-lipophilic balance, or ion-exchange interactions, among others. If they can perform more than one kind of interaction, they are considered mixed-mode sorbents, being the most common ones, the sorbents that combine ion-exchange and reversed-phase interactions [13]. These sorbents can be classified depending on the ion-exchange interaction

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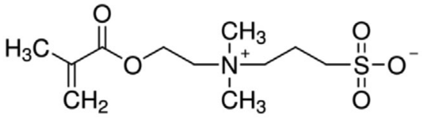
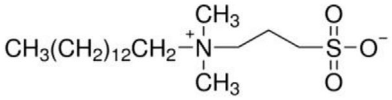
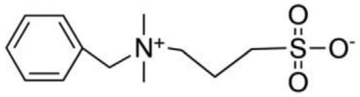
TABLE 1 | Name, zwitterionic additives, and their structures.

Name	Zwitterionic additives	Structure of the functional group
CW 20 M/ZW-1	2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide	
CW 20 M/ZW-2	3-(N,N-Dimethylmyristylammonio)propane sulfonate	
CW 20 M/ZW-3	3-Benzyldimethyl-ammoniopropane sulfonate	

they perform, the anion exchangers retain anionic compounds meanwhile the cation exchangers retain cationic compounds. The strong anion-exchange (SAX) sorbents are functionalized with quaternary amines and the weak anion-exchange (WAX) sorbents are functionalized with primary or secondary amines. In the same way, strong cation-exchange (SCX) sorbents and weak cation-exchange (WCX) sorbents are mainly functionalized with sulfonic and carboxylic acid groups, respectively, to retain anionic compounds [13].

There are severalexamples of mixed-mode ion-exchange commercial sorbents that are commercially available, being “Strata” and “Oasis” brands the most commonly used, which are polymeric based. In addition, silica-based sorbents are also commercially available, like the “Isolute” brand. Aside from the commercial ones, homemade sorbents have been developed in the recent years such as polymer-based materials with cation-exchange [14] and anion-exchange moieties [3, 15]. In the same way, silica-based materials have also been developed with cation-exchange [16] and anion-exchange [8, 17, 18] moieties. All of them have been widely applied with good performance; however, they are only functionalized with one type of ion-exchanger moiety, so they are only capable of extracting one type of compound, either cationic or anionic ones.

Moreover, some homemade sorbents have been synthesized with both anion- and cation-exchange moieties, so they are zwitterionic exchangers. There are examples of polymer-based sorbents [19–21] and silica-based sorbents [22–25]. For instance, the study performed by Wang et al. [24] modified silica with primary amines and carboxylic acid groups to extract acidic and basic analytes simultaneously from soft drinks, thanks to the dual functionalization. In that study, the performance was compared with Oasis WAX and Oasis WCX, showing similar extraction yields but Oasis WAX for the selective extraction of acidic compounds and Oasis WCX for basic compounds.

This type of sorbents are designed to extract ionizable compounds, compounds with acidic or basic behavior. An example of such compounds includes pharmaceuticals, whose determination in environmental samples has attracted growing interest. Pharmaceutical contaminants is a problem with increasing concern [26] because the presence of pharmaceuticals in environmental waters pose substantial risks for public health and aquatic ecosystems [27, 28]. Therefore, the quantification of pharmaceuticals in surface and wastewater water samples is relevant to evaluate the presence of these pollutants [29].

In the current study, three mixed-mode zwitterionic ion-exchange sorbents have been developed, characterized, and evaluated for the solid-phase extraction (SPE) of acidic and basic pharmaceuticals. A method based on the best performing sorbent was applied for the determination of the pharmaceuticals in environmental water samples (river, effluent, and influent wastewater) through liquid chromatography with high resolution mass spectrometry detection (LC-HRMS).

2 | Experimental

2.1 | Reagents and Standards

Zwitterionic functional groups 2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide, 3-(N,N-dimethylmyristylammonio)propanesulfonate, and 3-benzyldimethylammoniopropane sulfonate; and reagents used for synthesis: dichlormethane (DCM), acetone, trifluoroacetic (TFA), ammonium hydroxide, dichloromethane, acetic acid, formic acid, tetramethylortosilicate (TMOS), and methyltrimethoxysilane (MTMS) were purchased from Sigma–Aldrich (St. Louis, MO, USA). NaOH and HCl were acquired from Thermo Fisher Scientific (Milwaukee, WI, USA). HPLC grade acetonitrile (ACN) and methanol (MeOH) were purchased from Fisher Scientific (Steinheim, UK). A Milli-Q purification system (Millipore, Bedford, MA, USA) was employed to obtain ultrapure water. MS grade water and ACN were acquired from Carlo Erba (Val de Reuil, France).

Solid standards of five acidic pharmaceuticals: valsartan (VAL), diclofenac (DIC), clofibric acid (CLO), fenoprofen (FEN), and bezafibrate (BEZ), and five basic pharmaceuticals: propranolol (PRO), venlafaxine (VEN), metoprolol (MTO), trimethoprim (TRI), and atenolol (ATE) were acquired as pure standard (purity > 96%) from Sigma–Aldrich. Standard solutions of 1000 µg/L were prepared in MeOH and stored in the freezer (−20°C) in dark bottles. Working solutions were prepared weekly in water:MeOH (90/10, v/v) and stored in the refrigerator at 4°C in the dark.

2.2 | Preparation of Sol-Gel Carbowax 20 M/Zwitterionic Composite Sorbents

Sol-gel Carbowax 20 M/ZW composite material were prepared using the following pre-synthesis, synthesis, and post-synthesis processing steps: (a) hydrolysis of sol-gel precursors; (b) preparation of aqueous zwitterionic additives (presented in Table 1) solution; (c) dissolving Carbowax 20 M (CW 20 M) polymer in hydrolyzed sol solution, addition of zwitterionic additive solution, and initiating condensation process by adding methanolic ammonium hydroxide to the sol solution; (d) aging and conditioning of the bulk sol-gel composite monolith; (e) crushing, grinding, and drying of sol-gel CW 20 M/ZW composite sorbent; (f) disintegrating dry sol-gel CW 20 M/ZW into fine microparticles using mortar and pestle; (g) cleaning sol-gel CW 20 M/ZW in MeOH: DCM (50:50 v/v) in a sonicator for 30 min; and (h) drying sol-gel CW 20 M/ZW composite sorbent at 100°C for 8 h.

2.3 | Instruments and Equipment

The synthesis, characterization, and chromatographic equipment can be found in the Supporting Information.

2.4 | SPE Procedure

A total of 150 mg of the corresponding sorbent were packed on a SPE cartridge (Symta, Madrid, Spain) between two 10 µm polyethylene frits (Symta). Before loading the sample, 5 mL of MeOH and 5 mL of ultrapure water adjusted to pH 5 were used to condition it. After conditioning the sorbent, a volume of sample (100 mL for river samples and 50 mL for effluent and 25 mL for influent wastewater samples) adjusted to pH 5 was loaded into the cartridge (flow rate: 10 mL/min). The elution step consisted of passing 5 mL of 1% NH_4OH in MeOH. The eluate was evaporated to dryness (miVac Duo centrifuge evaporator [Genevac, Ipswich, UK]) and then, reconstituted with 1 mL of water/ACN (95/5, v/v). Prior to SPE, all samples were filtered using a 0.45 µm nylon membrane filter (Scharlab). In addition, wastewater samples underwent preliminary filtration with a 1.2 µm glass-fiber membrane filter (Fisher brand, Loughborough, UK).

2.5 | Chromatographic Conditions

The separation was performed with a Luna Omega Polar C_{18} 100 (150 × 3.0 mm, 5 µm particle size) column equipped with a precolumn (4 × 3 mm, 5 µm particle size) with the same filling supplied by Phenomenex (Torrance, CA, USA). The injection volume was 20 µL, the flow rate 0.4 mL/min, and the column oven was set at 30°C. The selected solvents for mobile phase were ultrapure water adjusted to pH 3 with HCl (solvent A) and ACN (solvent B). The gradient began with 5% of B, increasing the % of B to 60% within 6 min, then it was increased to 100% of B within 6 min, where it was held for 3 min before returning to the initial conditions in 1 min. The initial conditions were maintained for 3 min to stabilize the column. Two different wavelengths were used: ATE, MTO, DIC, and BEZ were measured at 230 nm; TRI, VEN, PRO, VAL, and CLO were measured at 210 nm.

In the case of LC-HRMS conditions, the chromatographic conditions were the same as LC-DAD except for "solvent A" which was substituted by water with 0.1% of HCOOH. Basic analytes were determined in positive ionization mode and acidic analytes were determined in negative ionization mode. Both conditions are presented in Table S1.

Two windows were employed for data acquisition, the first one for basic compounds in positive ionization mode and the second one for acidic compounds in negative ionization mode. Each window had two different scan events (range of 50–450 *m*/*z*). The first of them was a full scan at 50 000 FWHM (Full Width Half Maximum) and 250 ms for injection time. The second event consisted of a fragmentation scan at 10 000 FWHM with a collision voltage of 20 eV in the HDC and 50 ms for the injection time in both windows. The exact mass of the ions and their fragments can be found in Table S2.

3 | Results and Discussion

3.1 | Sol-Gel Sorbent Synthesis

Sol solution was prepared in a 100 mL polypropylene reaction vessel by adding TMOS, MTMS, and MeOH into the vessel. The mixture was vortexed for 3 min. Then, 0.1 M HCl was added to start the hydrolysis, the hydrolysis continued for 8 h at ambient laboratory conditions.

Zwitterionic additives (see Table 1), 2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide for ZW-1, 3-(N,N-dimethylmyristylammonio)propane sulfonate for ZW-2 or 3-benzyldimethylammoniopropane sulfonate for ZW-3, were weighed in a 50 mL centrifuge tube. Then, deionized water was added and the solution was vortexed until complete dissolution.

Carbowax 20 M (CW 20 M) polymer and zwitterionic additive solution were then added to the hydrolyzed sol solution, to facilitate the integration, the mixture was vortexed (3 min) and sonicated (30 min). Subsequently, 1 M NH_4OH was added to the sol solution and sonicated to remove trapped air bubbles.

The molar ratio between TMOS:MTMS: Zwitterionic additive:CW 20M:MeOH:HCl (0.1 M) and NH_4OH (1 M) used for the synthesis were 1:1:0.2:0.15:30:8:10, which was adopted from previous studies [18, 21].

The solution formed a transparent monolithic bed in an hour. The monolithic sol-gel bed was conditioned and aged at 50°C (24 h). After aging, the monolithic bed was crushed and transferred into a borosilicate glass drying vessel and dried at 100°C (12 h). Subsequently, the dried sol-gel CW 20 M/ZW composite sorbent was disintegrated into fine microparticles in a mortar and pestle. The fine particles were then rinsed with MeOH/DCM (50:50 v/v)

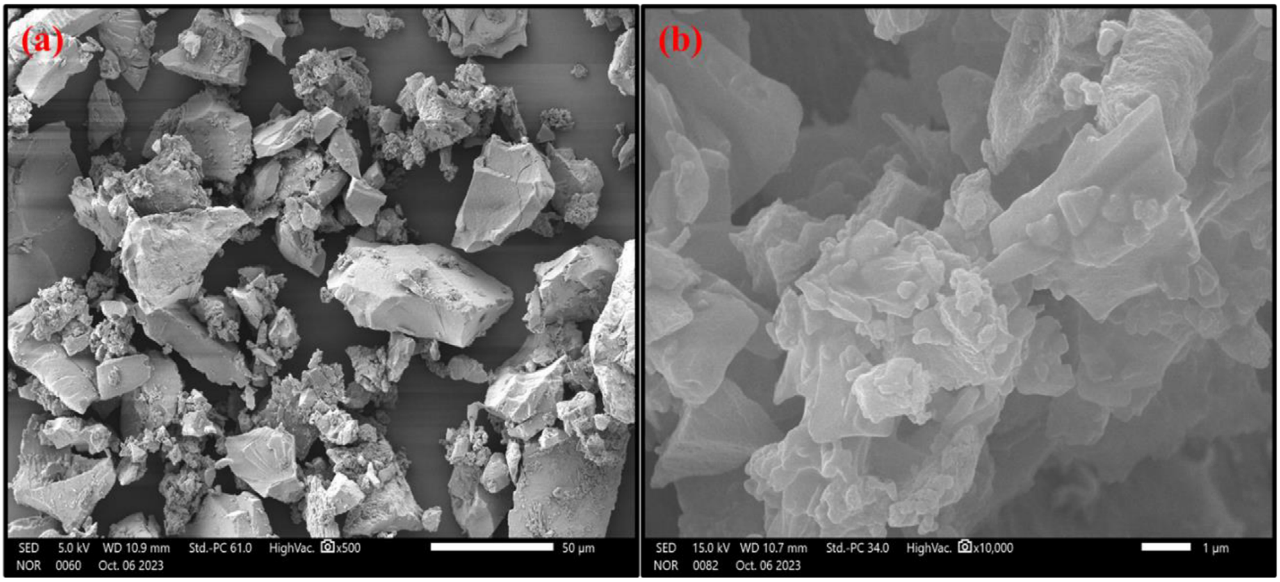


FIGURE 1 | Scanning electron microscopy images of sol-gel Carbowax 20 M/2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide composite sorbent at (a) 500× magnifications; (b) 10 000× magnifications.

and sonicated for 30 min. The sol-gel CW 20 M/ZW particles were then filtered and dried at 100°C for 8 h.

3.2 | Characterization of Sorbents

The three sorbents were characterized through scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR spectroscopy), and elemental analysis using scanning electron microscopy-energy dispersive spectroscopy (SEM-EDS). The characterization of CW 20 M/ZW-1 sorbent is discussed in the main text while the characterization of the two other sorbents (CW 20 M/ZW-2 and CW 20 M/ZW-3) are included in Supporting Information, since the characterization data for the three sorbents evaluated is similar.

3.2.1 | Scanning Electron Microscopy

Figure 1a,b presents SEM images of sol-gel Carbowax 20 M/ZW-1 sorbent. It can be seen in the SEM image at 500× magnifications (Figure 1a) the polydispersed particle sizes, that facilitates the packing in the SPE cartridge. Figure 1b presents the SEM image at 10 000× magnifications, where the sponge-like microstructure of the sorbent can be observed.

3.2.2 | Fourier Transform Infrared Spectroscopy

Figure 2 presents the FT-IR spectra of the main functional building blocks of sol-gel. The FT-IR spectra of CW 20 M is presented in Figure 2a. The most representative bands can be assigned to the alkyl chain of the polymer (2883 cm^{-1}), the C—H bending vibration (1342 cm^{-1}), the C—H twisting vibration (1240 cm^{-1}), and the C—O stretching vibration (1091 cm^{-1}) [30, 31].

The FT-IR spectrum of MTMS is presented in Figure 2b. The bands at 1276, 833, and 791cm^{-1} confirm the presence of Si-CH$_3$ from MTMS. Meanwhile the bands at 1188 and 1074 cm^{-1} are from Si-O-CH$_3$ in MTMS [30, 32].

The FT-IR spectrum of the zwitterionic additive, 2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide is presented in Figure 2c. The most representative bands from the additive are C═O bond in the ester group (1716 cm^{-1}), the stretching vibration of C—N$^+$ (1633 cm^{-1}), and the symetrical (1038 cm^{-1}) and asymmetrical (1165 cm^{-1}) stretching vibration of S═O in the sulfonate group [33, 34].

Figure 2d presents the FT-IR spectrum of sol-gel CW 20 M/ZW-1, many peaks that can be observed in this spectrum appeared in the spectra presented in Figure 2a–c. The peak at 2908 cm^{-1} can be assigned to the mentioned peak from CW 20 M to the alkyl chain of the polymer (2883 cm^{-1}), the peaks at 1722 cm^{-1} may correspond to the C═O bond in the ester group from the zwitterionic additive (1716 cm^{-1}) and the peak at 1171 cm^{-1} may correspond to the Si-OCH$_3$ band from MTMS spectrum (1188 cm^{-1}). Since several peaks from the building blocks appear in the FT-IR spectrum from the final product, the integration of the different building block components in the sol-gel composite can be considered succesfully accomplished.

3.2.3 | Scanning Electron Microscopy-Energy Dispersive Spectroscopy

SEM-EDS was applied to estimate the elemental composition of the sol-gel Carbowax 20 M/ZW-1 composite. Figure 3a,b presents the SEM image and EDS spectra. As the data revealed (inserted table), the primary components include C (38%), O (33%), Si (22%), S (5%), and N (2%). The presence of S and N reveals that the zwitterionic additive has been successfully integrated in the silica structure.

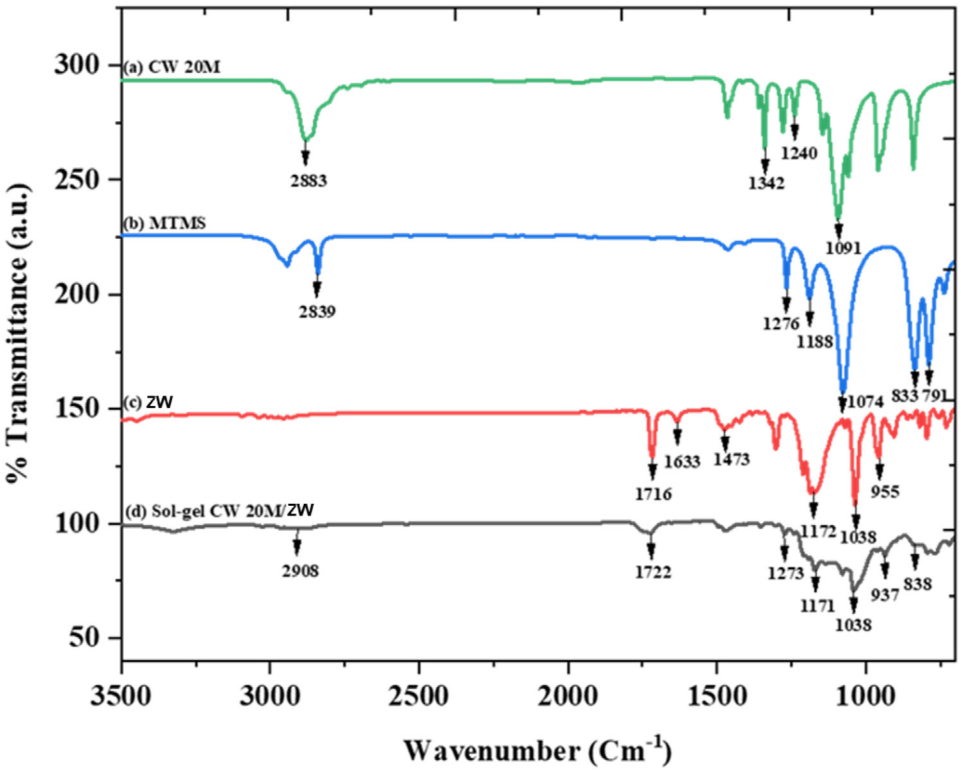
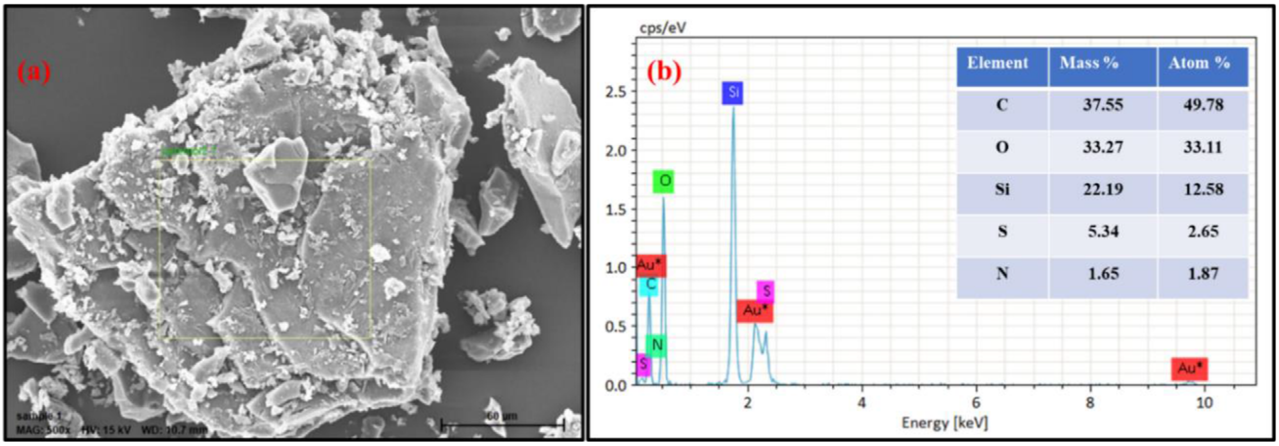


FIGURE 2 | FT-IR spectra of (a) pristine Carbowax 20 M polymer; (b) methyl trimethoxysilane (MTMS); (c) 2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide; (d) sol-gel Carbowax 20 M/2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide composite sorbent.



Element	Mass %	Atom %
C	37.55	49.78
O	33.27	33.11
Si	22.19	12.58
S	5.34	2.65
N	1.65	1.87

FIGURE 3 | Scanning electron microscopy-energy dispersive spectroscopy (SEM-EDS) images of sol-gel Carbowax 20 M/2-(methacryloxy)ethyldimethyl-3-(sulfopropyl)ammonium hydroxide (a) SEM image; (b) EDS graph with elemental composition in the inset.

3.3 | Evaluation of the Three Sorbents and Optimization of the SPE Protocol

The three synthesized sorbents (CW 20 M/ZW-1, CW 20 M/ZW-2, and CW 20 M/ZW-3) were evaluated for the SPE of the selected five acidic (CLO, BEZ, VAL, FEN, and DIC) and five basic (ATE, TRI, MTO, VEN, and PRO) pharmaceuticals. Based on previous experience with zwitterionic sorbents [22] and the pK_a of the analytes (Table S2), the initial conditions selected were a 25 mL of ultrapure water as loading step and 5 mL of 5% NH_4OH in MeOH followed by 5 mL of 5% CH_3COOH in MeOH as elution step. The three sorbents were evaluated with solutions adjusted at pH 3, 5, 7, and 9 to choose both the best performing sorbent and the optimal pH at the same time. $\%R_{SPE}$ was used to determine the best conditions and was calculated dividing the concentration obtained after the SPE by the theoretical concentration in ultrapure water.

Figure 4 shows the $\%R_{SPE}$ obtained for the three sorbents at pH 5 and Figures S5–S7 show the $\%R_{SPE}$ at pH 3, 7, and 9, respectively.

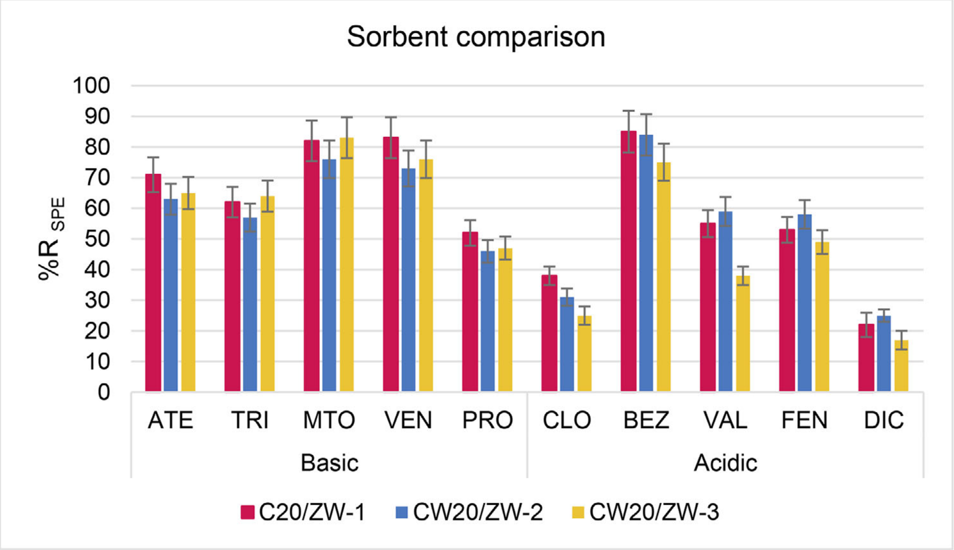


FIGURE 4 | Recoveries obtained when 25 mL of ultrapure water at pH 5 was loaded in the three different sorbents.

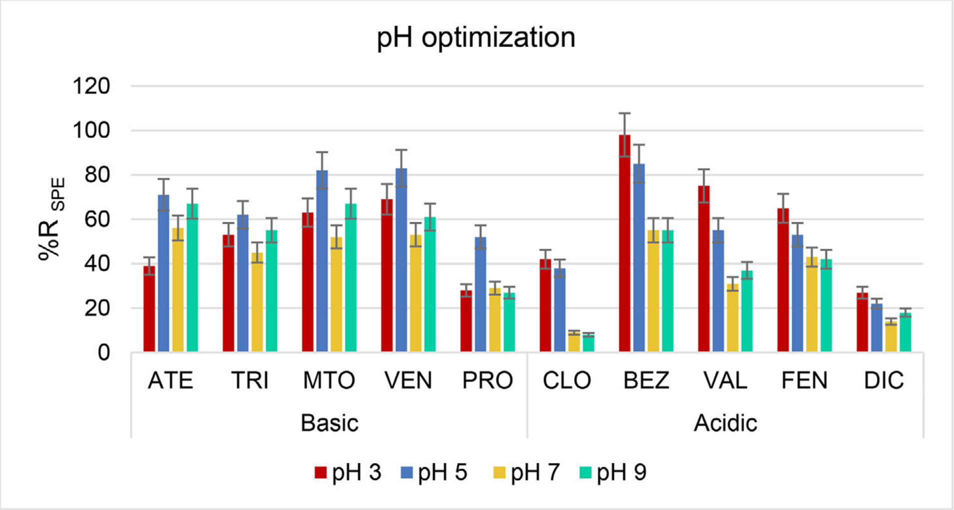


FIGURE 5 | Recoveries obtained when 25 mL of ultrapure water at different pH was loaded in sorbent CW 20/ZW-1.

It can be observed that the three sorbents provided acceptable values (> 50%) for most of the compounds, except for CLO and DIC. Because CW 20 M/ZW-1 presented the highest values for all the basic compounds and for some of the acidic ones (CLO and BEZ) at any pH, it was selected as the best performing sorbent.

For comparative purposes, Figure 5 shows the %R_{SPE} at pH 3, 5, 7, and 9 for CW 20 M/ZW-1. As shown in this figure, the optimal pH for the acidic compounds was pH 3, meanwhile the best pH for the basic ones was pH 5. However, for the basic analytes, the retention of ATE, MTO, and PRO at pH 3 were significantly lower than at pH 5, meanwhile, for the acidic ones, the differences between pH 3 and pH 5 were only remarkable for VAL (%R_{SPE} of 75% at pH 3 and 55% at pH 5). Therefore, the working pH selected was 5, at this pH both acidic and basic analytes are charged (pK_a can be observed in Table S1), thus enhancing the ion-exchange interactions with the sorbent. Wang et al. [24] also chose an acidic pH (pH 6) when determining acidic and basic compounds in soft drinks with a mixed-mode zwitterionic exchange silica sorbent.

During the selection of the best sorbent and pH, it was observed that the elution with acidified MeOH (5 mL of 5% CH_3COOH in MeOH) could be removed since all the analytes were eluted with the basic MeOH (5 mL of 5% NH_4OH in MeOH). Furthermore, it was observed that after successive extractions with the same cartridge, the performance of the sorbent decreased (%R_{SPE} decreased from 10% to 40% depending on the analyte). Considering that the basic elution might damage the sorbent, it was decided to evaluate the use of lower content of ammonia (1% NH_4OH) in MeOH. After these experiments, it was observed that the decrease in the percentage of NH_4OH prevented the material to be damaged without affecting the elution of the compounds (no observed decrease of the %R_{SPE}).

To increase the selectivity of the extraction, the addition of a washing step with MeOH was evaluated. The objective of this washing step was to remove the compounds retained through reversed-phase interactions and then, rinse the compounds retained through ion-exchange interactions in the elution step. Considering the previous experience with other silica-based sorbents functionalized with strong ion-exchange moieties [22, 35], 1 mL of MeOH was initially tested. Similarly to a previous study [22], the basic analytes remained retained in the sorbent but the acidic ones were rinsed with MeOH. This could be explained by the electrostatic repulsions that can occur due to the high concentration of charges. The charges of sorbent and analytes may involve that the retention through ion-exchange interactions of the acidic compounds is not strong enough to prevent their rinsing with MeOH. In our previous study [22], it was decided to maintain the washing step and only determine the basic analytes with high selectivity. However, in the present study, we removed the washing step and determined both acidic and basic analytes, despite partially sacrificing the selectivity. Thus, the optimized protocol did not include a washing step, which might be a limitation.

An increase in loading volume from 25 to 100 mL was evaluated to improve the preconcentration factor without observing significant losses in the recoveries. It should be noted that 100 mL was maintained when loading river samples but it was lowered to 50 mL for effluent wastewater samples and to 25 mL influent wastewater samples due to the complexity of these samples.

3.4 | Validation of the Method

Once the method was optimized, it was validated with LC-HRMS quantification in terms of apparent recovery (%R_{app}) at two levels of concentration, matrix effect (%ME), method detection (MDL) and quantification limits (MQL), accuracy (relative recovery), and precision (repeatability and reproducibility between days) with river, effluent wastewater, and influent wastewater samples.

The %R_{app} were calculated dividing the measured concentration after subtracting the blank concentration by the theoretical concentration. It was obtained spiking at two levels of concentration, 1 and 2 μg/L for river samples, 2 and 5 μg/L for effluent, and 4 and 10 μg/L for influent wastewater samples. As can be observed in Table 2, good recoveries were obtained in the three types of samples for most of the compounds. ATE and CLO were the analytes with lower recoveries; in fact, CLO presented low retention yields when loading ultrapure water samples (as can be observed in Figure 5) and this behavior was enhanced by the complexity of the samples. In the case of ATE, a significant decrease in the recoveries when working with more complex samples was already observed in a previous study [22], when the recoveries decreased from 94% (ultrapure water) to 40% (river samples). For the rest of the compounds, recoveries higher than 30% were observed for all of them except for DIC in influent wastewater samples, which can be explained by the high matrix effect (−84%). In the case of VAL in influent wastewater samples, the natural occurrence in the samples was higher than the concentration spiked, so the %R_{app} could not be calculated. Similar compounds were determined by Nadal et al. [19] with a polymeric mixed-mode zwitterionic exchange sorbent, obtaining recoveries ranging from 57% to 81% (river) and from 25% to 105% (effluent wastewater). Jaukovic et al. [36] determined pharmaceuticals in river and wastewater samples from Serbia applying Oasis HLB for the extraction and the recoveries obtained ranged from 26% to 121% (river) and from 45% to 107% in wastewater (either in effluent or influent).

The matrix effect was calculated using the following expression: $\%ME = (C_e/C_t \times 100) - 100$, where "$C_e$" denotes the concentration obtained by spiking (1 μg/L for river samples, 2 μg/L for wastewater samples) a non-spiked sample after SPE, subtracting the blank signal, and "C_t" denotes the theoretical concentration. A positive value indicates signal enhancement while a negative value indicates signal suppression. As can be observed in Table 2, low %ME were obtained for river samples, being lower than ±25% except for ATE (−31%) and TRI (−46%). Effluent wastewater samples suffered higher signal suppression, mainly for basic compounds, ranging from −41% to −49% for ATE, TRI, MTO, and PRO. For acidic compounds, the matrix effect was lower, being BEZ the most suppressed one (−30%). Attending to influent wastewater samples, the complexity of the sample caused higher suppression. Only PRO, CLO, and BEZ presented a %ME lower than ±35%, meanwhile VEN or DIC reached values of −62% and −84%, respectively. The lack of a washing step led to high-matrix effect values, especially when the complexity of matrices increased. Salas et al. [37] combined two commercial mixed-mode strong anion- and cation-exchange sorbents in one cartridge to extract similar compounds from environmental water samples. In their study, 15 mL of MeOH were used as washing step, obtaining %ME ranging from +5% to −36% (river), from −10% to −49% (effluent wastewater), and from +10% to −42% (influent wastewater). Thus, in spite of using such a high volume of washing solvent, the matrix effect was comparable to the values obtained in this study, except for the influent wastewater samples.

The accuracy of the method was evaluated as the relative recovery, which was obtained as the ratio between the calculated concentration after the correction with the apparent recovery and the theoretical concentration. It was obtained at two levels of concentration (1 and 2 μg/L for river samples and 2 and 5 μg/L for effluent and influent wastewater samples). The relative recoveries ranged from 88% to 111% (river), from 85% to 113% (effluent wastewater), and from 92% to 115% (influent wastewater). Relative recoveries were not obtained for ATE and CLO due to their low apparent recoveries.

The MDL and MQL were estimated applying the preconcentration factor and the apparent recoveries to the instrumental limits. The instrumental detection limit was determined as the concentration exhibiting a signal-to-noise ratio greater than 3, with one of the fragments yielding a signal exceeding 10^3 arbitrary units (AU). In addition, the instrumental quantification limit (MQL) was established as the lowest point on the calibration curves, ensuring a signal-to-noise ratio higher than 10. Table S3 presents the MDLs and MQLs. It can be observed that MDLs were lower than 5 ng/L. In the case of MQLs, all of them were lower than 12 ng/L except for FEN, whose limits were significantly higher. The low ionization yield of FEN produced high-instrumental limits that led to high-method limits.

TABLE 2 | Apparent recoveries (%R_{app}) at two levels of concentration and matrix effects (%ME) in river, effluent wastewater, and influent wastewater samples.

		River			Effluent wastewater			Influent wastewater		
		R_{app} high conc[a]	R_{app} low conc[a]	ME[a]	R_{app} high conc[a]	R_{app} low conc[a]	ME[a]	R_{app} high conc[a]	R_{app} low conc[a]	ME[a]
Basic	ATE	11	10	−31	18	20	−41	14	14	−53
	TRI	50	42	−46	61	60	−45	33	31	−58
	MTO	68	62	−25	81	81	−41	48	44	−54
	VEN	64	63	−21	64	59	−49	38	38	−62
	PRO	48	43	+14	59	53	−12	52	43	−31
Acidic	CLO	9	8	+4	9	11	−3	14	14	−16
	BEZ	75	65	−13	68	55	−30	64	67	−31
	VAL	69	78	13	65	88	−7	—[b]	—[b]	—[b]
	FEN	69	76	+14	83	72	−26	45	56	−51
	DIC	33	38	−4	33	32	−24	16	15	−84

[a] RSD ($n = 3$) < 14%.

[b] Natural occurrence higher than spiked concentration.

The precision evaluated as the repeatability (% RSD, $n = 4$) and the reproducibility between days (% RSD, $n = 4$) was obtained at 1 µg/L for river samples and 2 µg/L for wastewater samples. The repeatability was lower than 14% and the reproducibility between days was lower than 18% for all type of samples.

It should be born in mind that this study was conducted using different cartridges, which included different batches of the sorbent. In addition, the cartridge can be reused up to 50 times, which ensures the reusability of the sorbent.

3.5 | Analysis of Real Environmental Samples

River, effluent wastewater, and influent wastewater samples ($n = 3$) collected in the Tarragona region (Spain) were analyzed to determine the acidic and basic analytes. Quantification was performed applying external calibration curves, the previously obtained apparent recoveries, and the preconcentration factor. To confirm the presence of the compounds, the difference in the retention time should be less than 0.1 min, the mass error of the molecular ion must be less than 5 ppm, the signal of at least one fragment ion must be higher than 10^3 AU, and the relative intensities of at least one fragment ion and the molecular ion should be within ± 40% relative deviation (following the indications of 2021/808/EC) [38].

Table 3 shows the concentrations found in river, effluent wastewater, and influent wastewater and in brackets, the ranges of uncertainty for each type of sample. Starting with river samples, they showed the lowest concentration and some compounds were not detected (FEN and TRI in all samples, and PRO in some samples). It was possible to confirm the presence of DIC and VEN in all the samples analyzed. For MTO, PRO, and BEZ (in one of the samples), peaks were detected in the retention time of these compounds but the ratios between the fragment ions and the molecular ion were not in the range of acceptance. The highest concentration found was DIC with 401 ng/L. Nadal et al. [39] determined similar compounds in river samples from Ebro river, and found lower DIC concentrations, ranging from 23 to 30 ng/L, and higher ATE concentration, ranging from 8 to 45 ng/L. Klančar et al. [40] also determined several pharmaceuticals in river samples from Slovenia, and ATE, DIC, MTO, or TRI were detected at concentrations below the quantification limits which were 80, 1.6, 0.4, and 0.4 ng/L, respectively. Garrido et al. [41] determined some emerging pollutants in river samples in the south of Spain, among which ATE, TRI, CLO, and BEZ. ATE and CLO were not detected (MDL of 0.67 and 6.2 ng/L respectively), and similar concentrations than the present study of TRI and BEZ were found, ranging from < MDL (0.14 ng/L) to 25 ng/L and from < MDL to 139 ng/L, respectively.

In the effluent wastewater samples, all compounds were detected in at least one sample except for FEN. Regarding the ratios between fragment and molecular ions, they were acceptable for all compounds except for PRO in one sample. The compounds with higher concentration were VAL and DIC ranging from 881 to 11 847 ng/L and from 428 to 2938 ng/L, respectively. When Vergeynst et al. [42] quantified pharmaceuticals (DIC, TRI, and VEN) in wastewater samples from Belgium, TRI was not detected (MDL = 28 ng/L), meanwhile the concentrations of DIC and VEN were similar to the one found in the present study, ranging from 542 to 1391 ng/L and from 205 to 365 ng/L. When Zhang et al. [43] determined several pharmaceuticals in Chinese effluent wastewater samples, the average concentrations of TRI and VEN were lower than the present study, being 4.4 and 34.2 ng/L. In the case of MTO, the average concentration found was similar to the present study (165 ng/L).

Attending to influent wastewater samples, as expected, the concentrations were the highest among the three types of samples. All compounds except for FEN and VAL could be quantified since FEN had high quantification limits of the method and for VAL recoveries could not be calculated. The ratios between the

TABLE 3 | Concentrations found (ng/L) in river, effluent wastewater, and influent wastewater samples ($n = 3$).

		River	Effluent	Influent
Basic	TRI	< MDL	< MDL–1178 (184–202)	577–19 137 (57–1154)
	MTO	< MDL	89–178 (15–29)	326–1414 (53–231)
	VEN	22–27 (2–4)	206–1091 (30–163)	324–1123 (48–168)
	PRO	< MDL	< MDL–249 (2–33)	< MDL–1546 (6–170)
Acidic	BEZ	< MDL–81 (3–11)	48–422 (8–58)	204–1537 (24–211)
	VAL	< MQL–235(4–10)	881–11 847(184–2483)	—
	FEN	< MDL	< MDL	< MQL
	DIC	16–401 (2–45)	692–4666 (80–670)	1734–6456 (196–728)

fragment ions and the molecular ion were acceptable in all cases except for PRO in one sample. All compounds were present in at least one sample with concentrations above 1000 ng/L. Gilart et al. [44] determined similar compounds in wastewater samples from Tarragona region and MTO and TRI were quantified at similar levels of concentration (116–1857 and 97–155 ng/L, respectively). Vergili et al. [45] also determined pharmaceuticals in influent wastewater samples, and DIC concentration ranged from 810 to 4300 ng/L, meanwhile TRI and VEN were found at lower concentrations than in the present study (140–290 and 130–300 ng/L, respectively). When Van Nuijs et al. [46] determined MTO and VEN in influent wastewater samples from Belgium, concentrations of MTO were similar, ranging from 252 to 1190 ng/L. In the case of VEN, the concentrations found were lower (119–480 ng/L).

4 | Conclusions

Three novel mixed-mode zwitterionic ion-exchange silica-based sorbents were synthesized using only one single additive. The additive was a molecule with both quaternary amine and sulfonic acid groups, making it possible to introduce the strong anion-exchange and the cation-exchange moieties. In addition, silica demonstrated to be a good substrate to insert the functional groups as it could be observed in the characterization.

The optimized SPE protocol did not include a washing step based on methanol to be able to determine both acidic and basic compounds, but it limited selectivity of the developed method.

A method based on SPE followed by LC-HRMS applying the best performing sorbent was successfully developed and validated for the simultaneous determination of five acidic and five basic pharmaceuticals in environmental water samples. Most of the compounds were detected when the developed method was applied to the determination of the pharmaceuticals in river, effluent wastewater, and influent wastewater samples.

Author Contributions

Alberto Moral: experimental part, writing and editing. **Francesc Borrull**: funding acquisition. **Kenneth G. Furton**: supervision. **Abuzar Kabir**: experimental part, writing and editing. **Núria Fontanals**: supervision. **Rosa M. Marcé**: supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information file 1: jssc70280-supp-0001-SuppMat.docx